Remarks

Claims 9, 11, 12, 14, 23-26 and 44-53 were pending. Due to the previous species election, claims 11 and 24 are amended, and claim 25 is cancelled. However, Applicants request that the non-elected species be considered once the elected species is found to be allowable. Therefore, claims 9, 11, 12, 14, 23-24 and 44-53 are pending.

35 U.S.C. § 103(a)

Claims 9, 11, 12, 14, 23-26, and 51-52 are rejected under 35 U.S.C. § 103(a) as unpatentable over Isner *et al.* (WO 98/19712), an article from the Japan Financial Times (December 14, 1998), and Li *et al.*, (U.S. Patent No. 6,066,123) in further view of Morishita *et al.* (EP 0847757). In addition, claims 44-47, 50 and 53 are rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Isner *et al.* (WO 98/19712) in combination with an article from the Japan Finaneial Times (December 14, 1998) in further view of Morishita *et al.* (EP 0847757). Applicants disagree and request reconsideration.

It is asserted on page 7 of the Office action that there is no evidence of record to support Applicants' assertion that "one of ordinary skill in the art would reasonably expect the HGF gene administration to be short such as 1 to 2 days." There is ample evidence to support Applicants' assertion. For example, as described in the instant specification, and in paragraph 4 of the enclosed Rule 132 Declaration of Dr. Morishita (herein The Morishita Declaration), the half life of HGF is as short as about 10 minutes (see page 1, line 35). Furthermore, Li *et al.* (U.S. Patent No. 6,066,123, cited by the Examiner), teaches "1 to 2 days" as the shortest duration of gene product expression. These teachings and The Morishita Declaration support the Applicants' assertion or even shorter interval.

It is asserted on page 8 of the Office action that there is no evidence of record to support Applicants' assertion that "such findings would not have been readily expected from the short half-life of HGF." As discussed above, it is known in the art that the half life of HGF is as short as about 10 minutes. As stated in paragraph 4 of The Morishita Declaration, based on this knowledge, one skilled

in the art would not have expected that the effect of HGF gene to be maintained even after a few days or weeks, such as after 3 weeks or 5 weeks after its administration. The argument is not based on mere attorney argument, as asserted in the Office action.

It is further asserted on page 8 of the Office action that one of ordinary skill in the art would reasonably expect the effect of the HGF gene to be maintained after 3 to 5 weeks if it is administered *several* times during the 5 week period (emphasis added). However, this misses the point. The asserted prolonged effect was obtained after the HGF gene was administered only once during the experiment. The instant claims clearly recite "*once* every few weeks or few days". That multiple administrations can be provided is not the point, but instead the observation that one administration provides an unexpectedly prolonged effect. As stated in paragraph 6 of The Morishita Declaration and shown in Exhibit A, the inventors have demonstrated that administration of HGF gene once every few weeks (such as once every four weeks) is therapeutic for subjects having diabetic ischemic disease. That such infrequent administration would be therapeutic was not expected due to the short half life of HGF discussed above. This unexpectedly superior result rebuts any allegation that the cited references establish a *prima facie* case of obviousness.

On page 8 of the Office action, evidence is requested for the assertion "administering the HGF gene less frequently lowers costs therefore providing an unexpected benefit." Applicants' assertion is that lowering costs, in itself, is an unexpected benefit. Without the knowledge that the HGF gene can be administered less frequently, the skilled person had no way of expecting that administration costs could be reduced. Based on the short half-life of HGF, those skilled in the art would logically assume that more frequent administration was necessary, thus increasing the cost of the therapy. It is admitted in the Office action that one of ordinary skill in the art would understand that economics of using a product less frequently would result in a lower cost of using the product. This is a matter of course for even one of no ordinary skill in the art. Thus, no additional evidence should be required for the Applicants' assertion.

On page 9 of the Office action, evidence is requested for the assertion "that determining the dosages [that] would provide the desired therapeutic effect within such a wide dosage [range] requires a significant amount of experimentation by one skilled in the art." Morishita *et al.* discloses 0.1 to 100,000 μg (0.0001 mg to 100 mg), preferably 1 to 10,000 μg (0.001 mg to 10 mg). Morishita *et al.*

also discloses that diseases to be treated by HGF gene therapy include various arterial disorders (EP 0 847 767, column 5, lines 20-28). Thus, the broad dosage ranges cover those for various arterial diseases. In contrast, the claimed invention relates to a method for the treatment of diabetic ischemic diseases. Those skilled in the art appreciate that even armed with information disclosing broad dosages, the particular dose range that will treat a particular disease must be determined. As stated in paragraph 5 of The Morishita Declaration, a significant amount of experimentation was undertaken to determine the dose of HGF gene that would provide the desired therapeutic effects. The particular dosage or narrower range of doses that would be effective had to be determined, and was not obvious to those skilled in the art such as the inventors. In addition, as previously submitted (Melliere *et al.*, *Eur. J. Vasc. Endovasc. Surg.* 17: 438-41, 1999) and described in the instant specification (as well as paragraph 5 of The Morishita Declaration), it is known that angiogenesis hardly occurs and prognosis is unfavorable in diabetic ischemic diseases. As a result, a known therapy for arterial disorders may not be effective for treating diabetic ischemic diseases. Accordingly, it would not be routine for one skilled in the art to determine the HGF gene dosage for diabetic ischemic diseases.

It is asserted that the enclosed Morishita Declaration and arguments above provide the requisite evidence of Applicants' assertion of non-obviousness. In view of The Morishita Declaration and statements provided herein, Applicants request that the present remarks be considered and Notice of Allowance be issued. If the Examiner has any questions regarding this amendment, he is invited to telephone the undersigned.

Respectfully submitted,

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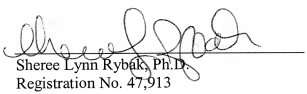
By 
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